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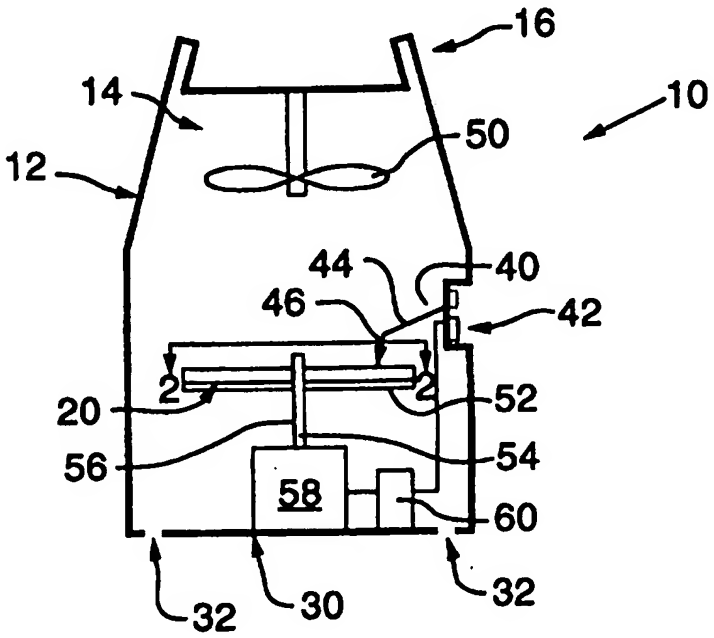
(54) Title: MEDICAMENT INHALER

(57) Abstract

A method of delivering a predetermined dose of a nicotine formulation through the lung alveoli and small airways into the bloodstream of a patient utilizes a portable inhaler containing the nicotine formulation. The portable inhaler may be used as a tobacco (e.g. cigarette) substitute. In one embodiment, individual dose capsules for a portable powder inhaler and their fabrication are also described.



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Title: MEDICAMENT INHALER

FIELD OF THE INVENTION

The present invention relates to an inhaler for dispensing a medicament into the lung. The invention also relates to a method for introducing nicotine into the lungs of a patient. The method may be used to assist the patient to withdraw from tobacco induced nicotine dependency. The invention further relates to the use of nicotine inhaled from a portable inhaler as a tobacco substitute (e.g. cigarette, cigar, pipe).

BACKGROUND OF THE INVENTION

In industrialized countries about one third of the adult population smokes cigarettes, resulting in a major avoidable cause of morbidity and mortality. Smoking is a contributory or causative factor in a number of diseases including respiratory diseases such as emphysema, chronic bronchitis, lung infections, and lung cancer; cardiovascular disease; gastric and duodenal ulcers; and cancer of the lung, oral cavity, larynx and oesophagus.

Most regular smokers become addicted to, or dependent upon, the pharmacological effects of nicotine in tobacco smoke. Nicotine is rapidly absorbed across the blood brain barrier and exerts a direct action on nicotine receptors in the spinal cord, autonomic ganglia and adrenal medulla. For more detailed information on the pharmacologic effects of nicotine see, for example, Oates and Wood, New Eng. J. Med. 319:1318, 1988.

Although nicotine is responsible for the addictive nature of cigarette smoking, most of the harmful health effects of smoking are attributable to other constituents in cigarette smoke (The Lancet, 337:1191, May 18, 1991). The combustion of tobacco in cigarettes results

in the production of up to 4,000 compounds and the inhalation of such unwanted by-products as tar, combustion gases and a range of carcinogens. Nicotine may be nitrosated to form highly carcinogenic tobacco-specific N-nitrosamines in tobacco smoke, or in the cured smokeless tobacco for use as chewing tobacco or snuff. It is an unfortunate feature of cigarette smoking that the negative consequences of nicotine addiction are largely manifested by the inhalation of toxic and carcinogenic materials generated by the combustion of tobacco.

The habit of smoking is based upon a pharmacological dependence on nicotine, an addiction comparable to that arising from the use of heroin. There are a number of acute symptoms of smoking cessation relating to nicotine withdrawal including irritability, anxiety, insomnia and a craving for nicotine. The addictive nature of nicotine poses a major obstacle to those who wish to quit smoking and a number of approaches have been developed to aid individuals in their efforts to stop smoking. The more successful of these involve therapy with nicotine substitutes such as chewing gum, nicotine patches, nicotine nasal sprays, nicotine vapour and the like. However, as discussed in more detail below, these approaches have met with limited user acceptance and limited success. In addition, there are individuals who are unable to stop despite repeated attempts, due to the addictive nature of nicotine. These individuals could benefit from a product which fulfilled their craving for nicotine, but did not have the same detrimental health consequences as cigarettes.

Smoking is a uniquely effective form of systemic drug administration. As nicotine enters the blood stream via the pulmonary circulation, it is speedily transported to the brain. Smokers achieve a rapid peak in nicotine levels in the blood within one or two minutes after finishing a cigarette. Nicotine substitutes generally contain nicotine in solid form, in a vapour or in solution. As nicotine is a base, these preparations are alkaline. The alkalinity of nicotine

substitutes is frequently increased, for example to pH 10, because at high pH nicotine is not ionized and ionization is known to impede the passage of nicotine across biological membranes (Burch et al., Am. Rev. Respir. Dis. 1989, 140:955).

With respect to nicotine gum, it is known that nicotine, even at an alkaline pH, is absorbed slowly across the mucous membranes of the oral cavity, so absorption by this route does not produce the very rapid increase in nicotine levels associated with cigarette smoking. Therefore, buccal absorption has proved to have limited use in simulating the effects of cigarette smoking and lessening the adverse symptoms of nicotine withdrawal. The rate of rise of nicotine levels in the blood which is achieved with chewing nicotine gum is much lower then that achieved by smoking cigarettes and the gum has been associated with gastrointestinal side effects, hiccups, mouth ulcers and sore throat. The amount of nicotine absorbed is also highly variable and is dependent upon the chewing and swallowing actions of the user over a prolonged period of time.

Nicotine patches are associated with skin irritation at the application site. The rate of absorption can vary with blood flow to the region where the patch is applied, which in turn can vary with temperature or the rate at which the user exercises. Both nicotine gum and dermal patches result in slow absorption of nicotine which is frequently not effective in satisfying the patient's craving for cigarettes. This may be one of the reasons for the lack of success of these forms of therapy in weaning subjects from smoking.

Self-propelled aerosols (also know as "pressurized aerosols") which contain nicotine in solution and a pressurized propellant have also been proposed as cigarette substitutes. An example is the self-propelled aerosol formulation of Jacobs in U.S. Patent No. 4,635,651. Such formulations are packaged in pressurized metered dose delivery systems. As shown in Jacobs, these delivery systems contain a water based aerosol formulation and a propellant,

such as pressurized freon, which are stored in a pressurized storage container. When the device is activated, the aerosol formulation is released at high speed from the pressurized storage container. The pressurized storage container is in flow communication with a delivery system. When the device is used by an individual, the user aims the delivery system into their mouth. The user then causes a valve of the pressurized storage container to be opened. When this valve is opened, the pressure inside the container forces a dose of medicament to be expelled at high speed from the container and into the user's mouth.

There are a number of problems with such pressurized aerosols. Pressurized aerosols require coordination on the part of the user who ideally should inhale at exactly the same time as the device is actuated in order to deliver the drug into the respiratory system of the user.

Failure to coordinate actuation of an aerosol inhaler and inhalation results in deposition of the aerosol in the oral cavities and upper respiratory tracts. In addition, even if the user properly aims the delivery device and coordinates the inhalation, the speed with which the aerosol is expelled from the device and enters the mouth causes much of the aerosol to impact on the throat and upper airways of the user. For the foregoing reason, the amount of nicotine entering the lower airways by using pressurized aerosols can not be accurately controlled. For example, devices such as the device disclosed in Jacobs in U.S. Patent No. 4,635,651 tend to expel some particles of about 40 μm. These particles would comprise agglomerations of particles and solvents. As the particles travel from the inhaler into the airway of the user, the particles would break up into smaller particles and some of the solvent would evaporate. However, even these smaller particles would still be at least about 10 μm as they travelled through the mouth of the user and would accordingly impact on the throat and upper airways of the user. Aerosols utilize nicotine which is in

solution. Since nicotine in solution has an alkaline pH which irritates the throat and upper airways, aerosols have poor acceptance by smokers (Burch et al., 1989, Am. Rev. Respir. Dis. 140:955).

Further, it is problematic to produce particles of an optimal size for absorption in the alveoli with a self-propelled aerosol. Jacobs in U.S. Patent No. 4,635,651 included a solid particulate component of defined size into a pressurized aerosol formulation of an inhalable nicotine solution.

SUMMARY OF THE INVENTION

It has been determined that a controlled dose of a medicament comprising at least one pharmaceutically acceptable nicotine preparation suitable for absorption into the blood stream of a person through the alveoli and lower airways of the person's lungs can be delivered to the alveoli and lower airways of the person's lungs by using a medicament suitable for absorption into the bloodstream of the person through the alveoli and lower airways of the person's lungs in a portable inhaler while causing only minimal noticeable irritation to the throat and upper airways of the person and, preferably without causing any noticeable or significant irritation. It has also been determined that a controlled dose of a medicament comprising a pharmaceutically acceptable nicotine preparation suitable for absorption into the bloodstream of the person through the alveoli and lower airways of the lungs can be delivered into the alveoli and lower airways of a person's lungs by an inhaler pursuant to this invention to mimic the pharmacologic effects of the nicotine administered by a cigarette, cigar, pipe or the like (hereinafter generally referred to as "cigarette") while minimizing or preventing the delivery of extraneous irritants or toxins into the oral cavity and respiratory airways. Preferably, the pharmaceutically acceptable nicotine preparation is suitable for absorption into the blood stream of a person through the alveoli and small airways of the person's lungs.

The present invention relates to a method of delivering a medicament including at least one nicotine formulation to a person comprising introducing a predetermined dose of a medicament including at least one nicotine formulation suitable for absorption into the bloodstream of the person through the alveoli and lower airways of the person's lungs, and preferably through the alveoli and small airways of the person's lungs, from an inhaler, into the alveoli and lower airways of the person's lungs, and preferably into the alveoli and small airways of the person's lungs.

The portable inhaler may comprise a housing, an air conduit within the housing adapted to conduct air flow to the person, a medicament comprising at least one pharmaceutically acceptable nicotine preparation suitable for absorption into the bloodstream of the person through the alveoli and lower airways of the person's lungs, and preferably through the alveoli and small airways of the person's lungs and means for introducing a predetermined dose of the medicament into the air conduit, whereby on activation of the inhaler and inhalation by the person, the medicament is introduced to the person's lungs.

The individual medicament particles, when they enter the air passageway of the user, may be up to about 10 μm in size, preferably up to about 7 μm, more preferably up to about 5 μm and most preferably up to about 3 μm. The nicotine formulation can be in the form of a powder or a liquid solution. The liquid solution must be converted to an aerosol. The nicotine powder may have a tendency to join together to form larger particles (eg. greater than about 10 μm) by various mechanisms (eg aggregation, agglomeration). If this is the case, then the force applied to the joined particles on inhalation may not be sufficiently great to break up the joined particles into constituent units sufficiently small so as to be entrained in the air inhaled by the user. Therefore, mechanical assistance is preferably provided to break up

such joined particles to constituent units sufficiently small so as to be entrained in the air inhaled by the user.

The nicotine formulation may be stored at atmospheric pressure as a powder or as a liquid solution. The liquid solution may be aerosolized using compressed fluid (preferably a gas). The compressed fluid that disperses the powder or that produces a liquid aerosol from the liquid solution of nicotine, may be contained in a reservoir chamber or be compressed by any mechanical means just prior to the dispersion of the powder or the aerosolization of the liquid solution. Further, the medicament may be stored under pressure provided that velocity reducing means is provided so that the momentum of the medicament particles upon inhalation is sufficiently low so as to permit the medicament to travel past the glottis and preferably to the small airways, which inhalers are referred to as non-pressurized inhalers. Such inhalers are in contrast to the pressurized portable inhaler of Jacobs wherein the medicament particles impact on the upper airway and cause excessive irritation to the user. The generation of the powder dispersion or of the liquid aerosol may be activated prior to the person taking the breath. Very high energy devices, such as ultra-sound, could be used to disperse the powder or to generate a liquid aerosol. Alternately, the nicotine formulation may be stored under high pressure.

The predetermined dose of nicotine may be from about 0.1 to about 10 mg and preferably from about 0.2 to about 2 mg of nicotine. In order to more closely mimic the pharmacologic effects of the nicotine administered by a cigarette, the inhaler may be adapted to provide a series of small doses of the nicotine preparation, such as from about 0.1 mg. to about 0.5 mg., over the period of time in which an individual would smoke a cigarette.

In an embodiment of the invention, the medicament may additionally comprise a pharmaceutically acceptable carrier,

binder, excipient, surface active agent, diluent, or a combination thereof.

In one embodiment, the medicament is dispersed by the person's breath. The inhaler may include means to mechanically assist the dispersion of the medicament. The means to mechanically assist the dispersion may include mixing means. The mixing means may comprise a non-rotatably mounted impeller. As the person inhales, the inhalation causes air to entrain the medicament and cause the medicament to flow past the impeller to assist in the dispersion of the medicament. Alternately, the mixing means may comprise a rotatably mounted impeller. As the person inhales, the inhalation causes air to entrain the medicament and cause the medicament to flow past the rotating impeller to assist in the dispersion of the medicament. The rotation of the impeller may be assisted by mechanical means such as by a battery operated motor.

Alternately, the medicament may be stored under pressure. Upon activation of the inhaler, the medicament is released from a pressurized container into the air. Depending upon the velocity at which the medicament is expelled from the container, the inhaler may include velocity reduction means so that, when the medicament is inhaled, the medicament is at a velocity sufficiently slow to be entrained in the air inhaled by the user. The velocity reduction means may comprise the use of air (in a chamber or otherwise) to create frictional drag on the medicament particles to slow the speed of these particles.

The nicotine may be any nicotine salt such as a sulphate or a bitartrate or a nicotine base, such as a nicotine oil formulation or mixtures thereof. These nicotine formulations may be absorbed, adsorbed or aggregated onto a suitable carrier or excipient. Alternately, the nicotine oil formulation may be encapsulated.

The invention also relates to a method of introducing a medicament comprising at least one nicotine formulation into the

lungs of a person using an inhaler having a housing having a first opening and a second opening, one of the first opening and the second opening being adapted to deliver the medicament to the mouth of the person and storage means for storing a medicament suitable for absorption into the bloodstream of the person through the alveoli and small airways of the person's lungs, the method comprising the steps of:

(a) releasing the medicament from the storage means and dispersing the medicament for inhalation by the person; and,

(b) inhaling the medicament.

The invention further relates to a method of introducing a medicament comprising at least one nicotine formulation into the lungs of a person using an portable inhaler having a housing having a first opening and a second opening, one of the first opening and the second opening being adapted to deliver the medicament to the mouth of the person and container means for receiving a medicament suitable for absorption into the bloodstream of the person through the alveoli and small airways of the person's lungs, the method comprising the steps of:

(a) delivering the medicament to the container means and dispersing the medicament for inhalation by the person; and,

(b) inhaling the medicament.

The method may be used to assist a person to withdraw from cigarette induced nicotine dependency through the introduction of a predetermined dose of the medicament into the alveoli and small airways of the person's lungs. In a preferred embodiment, the method is repeated at time intervals sufficient to reduce the negative effects of nicotine withdrawal. In a further preferred embodiment, where a person appears to be unable to stop smoking, the inhaler may be used as a cigarette substitute.

The inhaler according to this aspect of the invention may contain a single dose of a medicament which is intended to be inhaled

by the person in a single breath. Alternately, if the dosage which is required by a person is sufficiently great that it would cause irritation to the throat and upper airways of the person, a full dose may be located in the inhaler and the inhaler is preferably provided with by-pass air feed means for supplying air to dilute the air passing through the housing so as to reduce the concentration of the medicament in the air which is inhaled by the person.

Preferably, the by-pass air feed means is located near the opening which is adapted to deliver the medicament to the mouth of the person.

BRIEF DESCRIPTION OF THE DRAWINGS

These and other advantages of the instant invention will be more fully and completely understood by reference to the following description of the following drawings of an exemplary embodiment of the invention in which:

Figure 1 is a cross-section of an inhaler according to the instant invention;

Figure 2 is a top plane view along the line 2-2 in Figure 1;

Figure 3A discloses a cross-section of a further inhaler according to the instant invention;

Figures 3B and 3C disclose methods of how the inhaler shown in Figure 3A may be utilized by a person;

Figures 4A - 4D show a method by which a further inhaler according to the instant invention may be manufactured.

Figures 5A - 5D show a further embodiment of the inhaler according to the instant invention and the method of use of this further embodiment of the inhaler; and,

Figure 6 is a cross section of alternate inhaler which may be used pursuant to the instant invention.

DETAILED DESCRIPTION OF THE INVENTION

As hereinbefore mentioned the present invention relates to the use of a portable inhaler for dispensing a medicament comprising at least one nicotine formulation to the alveoli and the lower airways, and preferably into the alveoli and the small airways. In the art, "lower airways" is used to refer to the passages in the respiratory system which are downstream (upon inhalation) from the glottis. In the art, "small airways" is used to refer to the passages in the lungs which are less than about 2 mm in diameter. The inhaler may be used to deliver a predetermined dose of medicament comprising at least one nicotine formulation into the alveoli and lower airways, and preferably into the alveoli and the small airways, in a form which is sized for rapid absorption and which simulates the pharmacologic effect of a rapid increase in nicotine blood levels similar to that achieved by cigarette smoking. The rapid nicotine absorption is due to deposition of nicotine in the airways and alveoli of the lung where the medicament may be absorbed efficiently across the large surface area of the highly vascularized alveoli and the lower airways, and in particular the alveoli and the small airways.

The medicament to be drawn into the lungs may comprise one or more nicotine formulations. The medicament may be a powdered or liquid nicotine formulation. The nicotine is preferably in the form of a stable powder. The nicotine formulation may comprise a nicotine salt such as a sulphate or a bitartrate or a nicotine base, such as a nicotine oil formulation or pharmacologically active analogues or derivatives of nicotine or substances which mimic the effects of nicotine, either alone or in combination with other active substances. The medicament may be discrete particles or it may be absorbed, adsorbed or aggregated onto a suitable carrier or excipient. Alternately, if the medicament is a liquid, such as a nicotine oil formulation, the medicament may be encapsulated.

Nicotine is known to form salts with almost any acid and double salts with many metals and acids. Nicotine salts vary in their

ability to absorb water. It has been found that the ability of nicotine salts to penetrate into the distal regions of the lung, such as the lower airways and the alveoli and in particular the smaller airways and the alveoli, is based in part upon the size of the particles of the medicament and the degree of hygroscopicity of the medicament. For example, some nicotine salts are very hygroscopic. Accordingly, the particles rapidly increase in size when exposed to an airway of the person which is fully water saturated. The absorption of water by the particles increases the size of the particles and, for the reason set out herein, may alter the location of the deposition of the particles. By selecting a nicotine salt which is somewhat hygroscopic, and selecting the particles so as to be capable of being inhaled and transported to the alveoli and lower airways, and preferably to the alveoli and the small airways, a rapid increase in the blood level of nicotine may be obtained in a person. This rapid increase in blood level simulates cigarette smoking. Accordingly, the nicotine may be selected, based upon its hygroscopicity, to provide nicotine salt particles which are of the sufficient size to be transported to the distal regions of the lungs and, in particular, to the alveoli and lower airways, and preferably to the alveoli and the small airways. Preferred nicotine salts include sulphate and tartrate, chloride, bi-chloride, bitartrate, picrates, aipricrates, salicylates, picrolonates and dipicrolonates. More preferably, the salt is sulphate, bitartrate or mixtures thereof.

A medicament such as nicotine may be mixed with one or more pharmacologically acceptable binders, excipient or diluents, surface active agents, colouring or flavouring agents, suitable for inhalation. Examples of suitable solid diluents or carriers which may be used in the medicament include mannitol, dextrose and lactose.

In order to facilitate storage, handling and introduction of the medicament into the air conduit the medicament may be packaged in powdered form with a desiccant to prevent moisture absorption.

The medicament of the invention, if ionized (e.g. a nicotine salt), is poorly absorbed across the mucosa of the upper airways and is relatively non toxic to those surfaces. Surprisingly, the extensive cross-sectional area of the lower airways, and in particular the small airways, and the alveolar lining provides a large stable buffering environment for the ionized nicotine. As the nicotine is buffered in the lungs, the pH of the nicotine increases and the nicotine may be readily transported across the biological membranes in the lung. Thus, nicotine, whether acidic or basic, delivered into the distal regions of the lung is readily buffered and absorbed by the extensive airway and alveolar surfaces. It is the rapid and efficient absorption across the expansive buffered alveolar and airway surfaces which results in the steep rise in nicotine blood levels mimicking the pharmacological effect of cigarettes. The selective delivery to, and absorption across, the distal lung regions therefore mimics the pharmacologic effects of cigarette-derived nicotine while decreasing or eliminating the undesirable side effects of smoking or other nicotine substitution therapies.

The medicament doses of the present invention are intended for administration to humans and preferably contain from about 0.1 mg. to about 10 mg. of nicotine. The medicament can be prepared by known methods for the preparation of pharmaceutically acceptable compositions which can be administered to the airways of persons such that an effective quantity of nicotine is provided, which may be combined in a mixture with a pharmaceutically acceptable vehicle as hereinbefore mentioned.

In order for the nicotine in the medicament to be deposited in the alveoli and the lower airways, and preferably in the alveoli and the small airways, of the lung, the medicament enters the mouth of the user with a momentum sufficiently low to cause the medicament to be entrained in the air of the inhalation so as to follow the curvature in the pathways of the upper respiratory tract and be

carried to the lower airways, and preferably to the alveoli and the small airways of the lungs of the user. To achieve this result, the mass of the particles of the medicament (expressed in this application in terms of the size of the medicament particles given that the density of the particles is readily determinable) and the velocity of the medicament particles at the position from which it is inhaled must be in a defined range.

The nicotine is in a size range suitable for deposition on and absorption across the lower airways and the alveolar lining, and preferably the small airways and the alveolar lining, taking into account the amount of water which may be absorbed by the particles as they pass through the lungs. Larger particles, over about 7 μm, more particularly over about 10 μm (which have a higher mass) tend to be deposited in the oral cavity and upper airways. If the nicotine formulation contains a significant proportion of particles greater than about 7 μm, more particularly over about 10 μm, then the impaction of these nicotine particles on the throat and upper airways of the user during inhalation will cause irritation to the user and may make the product unacceptable to the user. It will be appreciated that some users are more sensitize than others to the irritation caused by these larger particles and, therefore, the amount of such particles which may be present in each dose will vary by user. As used herein, a medicament suitable for absorption into the bloodstream of the person through the alveoli and lower airways of the person's lungs does not include medicament particles that would cause significant irritation to the general public.

The particles grow in size as they are exposed to water in the atmosphere and in the airways of the user. For example, a 0.1 μm particle may increase to about 0.5 μm as it passes through the airways to the alveoli and smaller airways of a user. In order to have an appropriate mass, the individual medicament particles, when they enter the air passageway of the user, may vary in size up to about about

10 μm, preferably up to about 7 μm, more preferably up to about 5 μm and most preferably up to about 3 μm. However, it should be noted that the individual particles of the medicament may be joined together to form larger particles by various mechanisms (eg aggregation, agglomeration) If the medicament is a powder formulation, such joining may occur during the packing of the medicament container and/or during the storage of the medicament container. These larger particles, while they may be entrained by the air which enters the mouth of the user, may have a momentum which is too large to permit them to be transported past the glottis by the air which travels downstream from the glottis upon inhalation and will therefore tend to impact on the throat and upper airways of the user causing irritation to these areas. If the medicament contains a sufficient amount of these particles to cause such irritation, then these larger joined particles are preferably broken down into smaller component units. These smaller units may comprise individual medicament particles and/or such larger joined medicament particles from which some of the individual medicament particles have been removed so as to produce smaller joined particles. This reduction in size may be achieved when the large particles are expelled from the medicament container (eg. by the force applied to expel the particles from the medicament container) and/or by turbulence arising prior to and/or on inhalation (eg. by mixing means provided in the air flow conduit). Preferably, each dose of the medicament will contain a sufficiently small amount of particles greater than about 7 μm so as not to cause irritation or other undesirable side effects to the user. Twenty five percent of each dose may contain particles within the range up to about 7 μm, preferably more than about 35% of each dose, more preferably more than about 50% and, most preferably, more than about 70%.

To have an appropriate velocity, the air conduit of the inhaler is preferably sized to permit an air flow rate therethrough of

up to about 2 L/s, preferably up to about 1 L/s and, more preferably up to about 0.5 L/s upon inhalation by the person. Preferably, the medicament may be entrained in an air flow created by a normal or a less than normal inhalation.

Pursuant to the invention, the inhaler provides a predetermined dose of a nicotine medicament to the lung. The dose should be physiologically acceptable for administration to humans by this route of administration. The dose of nicotine delivered to the lungs may be from about 0.1 to about 10 mg, preferably from about 0.2 to about 3 mg, more preferably from about 0.2 to about 2 mg, and most preferably about 1 mg as a total dose in any one treatment. However, one treatment may consist of multiple inhalations of a smaller dose over a period of time thus more closely simulating the act of smoking and minimizing the irritant effect of nicotine impaction in the mouth and throat. Accordingly, in order to more closely mimic the pharmacologic effects of the nicotine administered by a cigarette, the inhaler may be adapted to provide a series of small doses of the nicotine preparation, such as from about 0.1 mg. to about 0.5 mg., over the period of time in which an individual would smoke a cigarette, typically from about 1 to about 10 minutes.

The use of the instant invention allows a person to achieve a rapid increase in nicotine blood level which effectively simulates cigarette smoking.

The inhalation of the medicament is achieved by the person's own breath. This breath may also serve to stir a powdered medicament in order to disperse it, and/or to activate any kind of system that will, in turn, assist the dispersion of the medicament. The powder dispersion can be assisted by any mechanical or electrical means, such as a battery operated impeller or vibrator. The dispersion of a powder or liquid formulation can also be assisted by the application of compressed air or gas to the formulation. The means

that assists the dispersion may be activated prior to the person taking the breath.

Various types of portable inhalers are known in the art. Such inhalers may have a housing, an air conduit adapted to conduct air flow to a person, and means for introducing a medicament into the air conduit. See, for example, U.S. Patent Serial No. 4,524,769 to Wetterlin; Bell et al., J. Pharmaceut. Sci. 60:1559, 1971; Newman et al., Eur. Res. J. 2:247, 1989; and Clark, A.R., Aerosol Science and Technology, Vol. 22, No. 4, 374-391, 1995. While various portable inhalers may be used in accordance with this invention, it will be appreciated that the exact inhaler which is used is preferably chosen based on the particle size range of the individual particles of the medicament, the particle size distribution of the individual particles of the medicament, the nature of the medicament (i.e. whether the medicament in a liquid or a solid formulation) and the degree to which the individual particles join together. If the medicament is in a form wherein the individual particles do not join together to any significant degree, then the medicament must be of a particle size range and distribution suitable for travelling to the alveoli and lower airways, and preferably to the alveoli and small airways, of the lungs of the user. If the medicament is in a form wherein the individual particles tend to join together to form a significant number of large particle, or if the medicament is a liquid formulation, then according to the preferred embodiment, means is provided to produce medicament particles which, at the point the medicament reaches the airways of the user, are of a particle size range and distribution suitable for travelling to the alveoli and lower airways, and preferably to the alveoli and small airways, of the lungs of the user. It will be appreciated that, depending on the size of the individual medicament particles and the inhaler which is selected, it may not be necessary to completely break up such joined particles to provide an aerosol comprising the individual medicament particles.

For example, if the medicament when inhaled contains few particles greater than about 2 μm, and the particles generally do not join together, then a much higher rate of inhalation may be used than if the medicament when inhaled contains a large percentage of particle in the range 2 μm to 7 μm. As will be appreciated from the following discussion, a mechanically simpler inhaler may be used if the medicament when expelled from the medicament storage container contains a high percentage (eg. 50%) of the dose as relatively small particles (eg. up to about 5 μm). Such particles may be entrained in air flowing at a higher rate without significantly impacting on the throat and upper airways of the user. Thus, the inhalation may be used to assist the break up of any joined particles. If the medicament comprises individual medicament particles within the desired size range but, the dose when expelled from the medicament storage container, contains a relatively large percentage (eg. 50%) of the dose as particles which are relatively large (eg. 5-10 μm), then a low velocity release inhaler which includes means to disperse, or to assist in such dispersion is preferably used so that, when inhaled, the joined particles have been sufficiently dispersed so as to reduce to a tolerable level, or preferably eliminate, irritation to the user.

Inhalers deliver medicaments to a position from which the user may inhale the medicament. As opposed to pressurized aerosol inhalers (e.g. Jacobs), the inhalers used pursuant to the instant invention deliver the medicament to the position from which the user may inhale the medicament at a velocity which is sufficiently slow so that the medicament may be entrained in the air upon inhalation by the user and transported past the glottis by the air which travels downstream from the glottis upon inhalation. Preferably, the medicament is carried to the smaller airways. The velocity of the medicament at the position from which it may be inhaled is preferably approximately equal to or lower than the velocity of gas during a normal, or part of a normal, inhalation so that most, if not all, of the

medicament released by the inhaler is entrained in the air upon inhalation by the user and transported past the glottis. Accordingly, while the medicament may have some forward velocity (i.e. in the direction of the airways of the user) when it is inhaled, the inhalation of the medicament is achieved, at least to a large degree, by the person's own breath. Such devices are referred to as "breath-activated" inhalers.

It will be appreciated that the velocity of the medicament prior to being delivered to the position from which it may be inhaled may be substantially greater that the velocity at the position from which it may be inhaled. Accordingly, as discussed in more detail below, the medicament may be in the form of a powder that is released from a storage container and held effectively stationary in a chamber until inhalation. Alternately, the medicament may be stored at high pressure so that the medicament travels at a high velocity when expelled from the container. Pursuant to this embodiment, the high pressure is used to deliver the medicament to the position from which it may be inhaled. The inhaler includes velocity reduction means so that by the time the medicament reaches this position, its velocity has decreased to within the desired range of velocities. The velocity reduction means may comprise the use of air (in a chamber or otherwise) to create frictional drag on the medicament particles to slow the speed of these particles. As the medicament travels from the storage chamber to the position from which it may be inhaled, the high velocity assists in the dispersion (break up) of the medicament particles.

Referring to Figure 1, inhaler (10) generally comprises a hollow housing (12) with an air conduit (14). One end of the air conduit (16) is adapted for insertion into the mouth of a person. Such inhalers have means for introducing the medicament into the air conduit, for example a rotatable disc (20) having spaced containers (22) of medicament which can be rotated to introduce a single dose of

medicament into the air conduit (see Figure 2). Containers (22) may be in the form of capsules, blister packs or any other similar container. In an alternate embodiment, it will be appreciated that containers (22) may contain multiple doses of medicament. In a further alternate embodiment, a single container may contain multiple doses (eg. 100 doses) of medicament. According to such an embodiment, each activation of the device causes a predetermined dose of medicament to be delivered to the chamber in the inhaler from which the medicament may be inhaled. Referring to Figure 1 in more detail, housing (12) has a bottom surface (30). Bottom surface (30) is provided with air inlets (32). Air inlets (32) are sized to provide an appropriate amount of air into inhaler (10). As the air enters inhaler (10), it travels past rotatable disc (20) and exits through end (16). In use, the person inserts one end of the air conduit into their mouth and inhales. Conduit (10) thus acts as a chamber to hold the medicament at a position from which it may be inhaled by the user. The turbulent airstream created in the air conduit by the person's inspiration fluidizes the medicament to produce a cloud of medicament particles which are carried into the lung with the inhaled air.

Inhaler (10) also includes means (40) for opening spaced containers (22) in a controlled fashion. As shown in Figure 1, inhaler (10) includes actuator button (42). Button (42) is movable between a first position as shown in Figure 1 and a second position which is shown in dotted outline in Figure 1. Button (42) is connected to extender arm (44). Attached to the distal end of extender arm (44) is piercing member (46). Piercing member (46) has a sharpened edge so that, when actuated, it will pierce spaced container (22) thus opening the container and allowing the medicament to be fluidized by the passage of air over the disc. Extender arm (44) and piercing member (46) are configured such that the sharpened edge of piercing member (46) is positioned adjacent the circle defined by spaced containers (22). When actuator button (42) is moved to the position shown in dotted

outline, piercing member (46) is moved so as to open spaced container (22).

Such inhalers are designed to dispense the medicament to the person without the use of any mechanical assistance to assist in the dispersion of the medicament in the air which is drawn into the lungs of the person. Such inhalers may be used if the medicament particles when positioned in conduit (10) are relatively fine and have a small particle size distribution, eg. the medicament comprises a high percentage (eg. 50%) of the dose as relatively small particles (eg. up to about 5 μm). Examples of such inhalers include the ROTAHALER™, CYCLOHALER™ and INHALATOR™ inhalers. See also United States Patent No. 4,811,731 for the DISKHALER™ which is incorporated herein by reference.

Most inhalers currently in use for the treatment of respiratory disorders have low resistance so that sufficient air flow can be generated by persons having impeded respiratory capacity and obstructed airways, resulting, for example, from an asthmatic attack. However, the high flow rates generated by users not having obstructed airways could cause larger particles (approximately greater than about 5 μm to about 10 μm) to impact against the back of the upper airway. If the medicament contains a large percentage of the dose (eg. greater than about 25%) as such larger particles and these particles tend not to join together, then the inhaler preferably restricts the velocity of air exiting the inhaler so as to limit the velocity of the medicament as it enters the airways of the user.

Alternately, the medicament particles may tend to join together to produce large joined particles (approximately greater than about 5 μm to about 10 μm) requiring a lower velocity of inhalation to avoid irritation of the throat and/or requiring turbulence and/or mechanical assistance to disperse, or assist in the dispersion of, the joined particles. Accordingly, if the medicament comprises a large percentage (eg. more than about 25%) of the dose as such larger

particles, it is preferred to use an inhalation device with mechanical assistance to disperse (break up), or assist in the dispersion (break up) of, the medicament.

Accordingly, mixing means which may serve two functions may be provided. First, to restrict the cross-sectional area of the air conduit so as to reduce the flow rate of air thereby decreasing impaction at the back of the throat particularly in the case of users not having obstructed airways. Secondly, to produce turbulence in the air flow to break up joined particles of the medicament which may be present in the inhaler prior to inhalation.

For example, as shown in Figure 1, inhaler (10) may be provided with mixing means (50) which is mounted at end (16). Air passing by mixing means (50) is disrupted so that joined particles of the medicament which might be formed are disrupted. Mixing means (50) may be a non-rotatably mounted impeller or other means which will cause a disruption in the air stream as the air passes thereover thus helping to disperse the medicament. An example of such inhalers include the TURBUHALER™ inhaler (United States Patent No. 4,907,583 which is included herein by reference). Alternately, mixing means (50) may be a rotatably mounted impeller or other obstruction means which rotates as the person inhales so as to assist the dispersion of the medicament. An example of such inhalers include the SPINHALER™ inhaler. See also United States Patent No. 3,831,606 which is incorporated herein by reference.

Preferably, in order to further assist in the dispersion of the medicament, mixing means (50) may be mechanically assisted by, for example, a battery operated motor. An example of such a device is disclosed in United States Patent No. 5,327,883 which is incorporated herein by reference.

In summary, suitable inhalers include traditional dry powder metered dose inhalers such as the DISKHALER™, the ROTAHALER™, the CYCLOHALER™ and the INHALATOR

inhalers which rely only on the person's inspiratory power to deliver and break up the medicament for inhalation. More sophisticated inhalers also include dry powder inhalers which provide mechanical assistance to break up, or to assist in the break up of, the medicament. The mechanical assistance may be in the form of a fixed impeller positioned in the path of the medicament as the medicament is inhaled, such as the TURBUHALER™ inhaler. Alternately, the mechanical assistance may be in the form of a rotating member, such as an impeller (eg. the SPINHALER™ inhaler).

More preferably, the inhaler is a low velocity release inhaler. Medicaments released by such inhalers are either effectively stationary at the point from which they are inhaled, or they are travelling at a velocity sufficiently slow so that particles as large as 5 to 10 μm may be entrained in the air inhaled by a user. Medicaments which may be used with such inhalers include liquid formulations and powder formulations wherein the medicament particles are relatively small but tend to join together. Such inhalers typically include mechanical means to disperse (break up), or to assist in the dispersion (break up) of the medicament.

To achieve the dispersion of the medicament particles while maintaining the medicament particles at a low velocity, low velocity release inhalers generally rely completely, or at least substantially, upon energy which is imparted to the system other than through the movement of air caused by inhalation by the user. One means which may be used to impart energy to the system is pneumatic pressure. In such inhalers, a metered does of medicament is discharged with the aid of a small compressed air pulse. An example of such a device is Galli (Patent Application WO 93/18812). As exemplified in Figure 6, the inhaler has dosage chamber 100. Dosage chamber 100 is isolated from the medicament container 106 by spring loaded plug 102. Medicament may be loaded into dosage chamber 100 by means of broom 104. Thus, once filled, dosage chamber 100 has an air tight

separation from medicament container 106. Dosage chamber 100 is in air flow communication with compression chamber 108. Positioned beneath compression chamber 108 is piston 110 which is situated on top of spring 112. Compression of plunger 114 by the user causes spring 112 to compress. Further compression of plunger 114 releases piston 110 which snaps upward into compression chamber 108 thus producing a jet of compressed air which is channelled into dosage chamber 100. This jet of air causes the medicament to be dispersed and to pass through nozzle 116 which is provided with a check valve 118. The jet of air disperses the medicament to the air surrounding nozzle 116. Alternately, as shown in dotted outline in Figure 6, a chamber may be positioned in flow communication with nozzle 116. Pursuant to this embodiment, the user may actuate plunger 8 causing the medicament to be expelled into chamber 124. The chamber acts as a receiving chamber to collect the dispersed medicament and, in addition, to allow the medicament to slow down to a sufficiently slow velocity or, to in fact become stationary. Thus the chamber acts as a velocity reduction means. Alternately, other devices that obstruct the air flow passage and thus act to decrease the velocity of the air carrying the medicament may be used. The user may then inhale via nozzle 122. As the user inhales, carrier air may be fed into the chamber via nozzles 120. Thus, mechanical means may be used to disperse the medicament and the inhalation by the user merely entrains the particles and is not required to disperse the particles. The high pressure which is used to deliver the medicament to the position from which it may be inhaled is sufficiently great to effectively disperse the particles. Alternately, it will be appreciated that the chamber may be configured so as to permit the inhalation to further assist in the dispersion of the particles.

In a further embodiment, it will be appreciated that instead of using a spring actuated mechanism, the medicament in the inhaler may be stored under pressure. Pursuant to this alternate

embodiment, the pressure which is maintained in the medicament storage container is used to deliver the medicament to chamber 124. Once again, as the medicament travels from the storage chamber to chamber 124, the high velocity imparted to medicament by the pressure from the storage chamber disperses, or assists in the dispersion of, the joined medicament particles. Further, by the time the medicament is delivered to chamber 124, its velocity is decreased to within the desired range of velocities.

Low velocity release inhalers may also use more sophisticated forms of mechanical assistance including aqueous atomization (the use of hydraulic amplification to generate high liquid pressures, eg. 400 bar, to atomize a medicament), ultrasound and the use of meshes driven by piezoelectric crystals to deaggragate the medicament. These inhalers deliver the medicament to a chamber from which the person may inhale the medicament or they may expel the medicament from the inhaler at a sufficiently low velocity to permit the medicament to be entrained with the air inhaled by the user (compared to the pressurized inhaler of Jacobs).

As a means of regulating dosage, or as a means of regulating the frequency with which a dosage may be administered, it may be desirable to include means to limit the frequency with which inhaler (10) may be utilized. For example, as shown in Figure 1, rotatable disc (20) may be mounted on plate (52) which is attached to axle (54). Axle (54) has one end (56) which is attached to electric motor (58) powered by a battery (not shown). Rotation of motor (58) causes axle (54) to rotate thus rotating rotatable disc (20). Motor (58) is calibrated so that each activation of motor (58) causes rotatable disc (20) to move a sufficient distance to place a new spaced container (22) adjacent piercing means (46). Actuator button (42) is connected to timing means (60). Accordingly, when a person utilizes inhaler (10), button (42) is moved to the position shown in dotted outline in Figure 1.

If the amount of nicotine contained in a single dose is designed to simulate an entire cigarette, then timer (60) may be preset so as to allow a further dose to be taken only after a reasonable period of time (e.g. 20 to 30 minutes) has elapsed. Timer (60) is conventional and is connected to and actuated when button (42) is pushed. Timer (60) cuts off power to motor (58), for example, two seconds after button (42) is pushed (to allow the motor enough time to advance disc (20) by one step) and keeps the power to motor (58) cut off until timer (60) has counted down the desired time (which can be made adjustable).

If each nicotine dose is made equivalent only to that obtained by one or two puffs from a cigarette, then timer (60) would normally not be needed. However, if desired, timer (60) may be preset to allow a plurality of doses to be taken over a relatively short period of time to simulate the nicotine levels which are achieved when an individual smokes a cigarette. For example, timer (60) could be provided and set to permit a desired number of doses (puffs) within a preset time (for example 5 to 10 doses within, for example, ten to fifteen minutes), and then to cut off power to motor (58) until a selected time interval (e.g 20 to 30 minutes) has elapsed. By adjusting the number of doses allowed in each period and the time intervals between the periods, the total nicotine dosage can be controlled and, if desired, gradually reduced to wean the person from his/her nicotine additions.

Alternatively, timer (60) can be set simply to count the time between doses even when one dose simply simulates one or two puffs on a cigarette.

In accordance with one embodiment of the invention a method of assisting a person to withdraw from cigarette induced nicotine dependency is provided. The method comprises delivering a medicament comprising one or more nicotine formulations suitable for absorption into the bloodstream of the person through the alveoli and lower airways of the person's lungs, and preferably the alveoli and

small airways of the person's lungs, from an inhaler to the alveoli and lower airways of the person's lungs, and preferably the alveoli and small airways of the person's lungs, for use by the person as a cigarette substitute.

When smokers attempt to stop smoking the recidivism rate is high due to the negative symptoms of withdrawal from nicotine addiction. Replacement therapy with cigarette substitutes is designed to lessen the impact of nicotine withdrawal and to assist a person in withdrawing from cigarette induced nicotine dependency. Cigarette substitutes are suggested as a replacement for cigarettes during the withdrawal period. The optimal replacement therapy will involve reproducing the sharp increase in nicotine levels achieved by cigarette smoking in order to effectively suppress the withdrawal symptoms. Successful withdrawal from smoking may require the use of inhalers according to this invention over a period of time during which inhalers are used to deliver successively smaller nicotine doses until complete withdrawal may be effected.

In order to effect a controlled withdrawal from nicotine the present invention provides an inhaler to deliver a predetermined dose into the distal regions of the lung. The predetermined dose is introduced into the air conduit from where it is efficiently drawn deep into the lungs. The size of each individual dose may therefore be accurately controlled.

In a preferred embodiment the minimum time interval between doses is also controlled to prevent the person from receiving an overdose of nicotine. The timer may be set to enforce time periods of from 5 minutes to about 2 hours. If the dosage is set to represent a puff of a cigarette, then the timer may have a first setting to permit several dosages to be taken over a period of a few minutes and a second setting to prevent a second plurality of dosages being taken before the expiry of from 5 minutes to about 2 hours. Accordingly, the present invention provides a highly controlled yet flexible method of

assisting a person to withdraw from cigarette-induced nicotine dependency by providing controlled doses of nicotine having a pharmacologic effect similar to that of cigarette smoke without the adverse side effects. The act of inhaling from a device in the mouth may also provide persons with a short-term behaviour substitute for inhaling a cigarette. In some cases where a person is unable to stop smoking, then the inhaler may be used as a replacement for cigarettes or cigarette substitutes.

As stated above, the recidivism rate is high due to the addictivness of nicotine. The high recividism rate is due to dependance on nicotine which is contained in tobacco and not to dependance on tobacco. For some people, the use of the inhaler according to the instant invention in accordance with an appropriate schedule may not enable them to eliminate their nicotine dependance. However, the inhaler described herein provides a cleaner source of nicotine (eg. without nitrosamines and other carcinogens present in the tar of cigarette smoke) which may be delivered to the lower airways and alveoli of the user pursuant to the method of the instant invention. As such, the inhaler may be used as a long term replacement for tobacco.

According to another embodiment of this invention, the inhaler may be used to deliver predetermined doses of nicotine to a person for various other reasons. Nicotine is an effective stimulant. The health problems associated with cigarettes are due to the other chemicals and compounds which are present in tobacco. The method of this invention permits controlled doses of nicotine to be delivered to a person. Accordingly, the method may be used to provide nicotine to a person as a stimulant, to increase vigilance or overall performance (eg. accuracy, speed), to control weight or assist in weight loss, or to assist in the treatment of Alzheimer's Disease, Parkinson's Disease or inflammatory bowel disease.

An alternate inhaler for delivering a medicament to the lungs of a user is shown in Figure 3A. Inhaler (70) may comprises a longitudinally extending housing having a first end (72) and a second end (74). As will become more apparent below, inhaler (70) may also include filter (76). A stopper (78) is positioned in each of ends (72) and (74).

Inhaler (70) may be of any particular shape. As shown in Figure 3A, the inhaler may comprises a longitudinally extending cylinder so as to simulate the shape of a cigarette. One of ends (72) and (74) is adapted to deliver a medicament to the mouth of a person. The other of ends (72) and (74) may be of any particular shape.

Inhaler (70) is preferably manufactured from an air impervious or air impregnable material. Preferably, inhaler (70) is also made from a material which would be effectively electrostatically neutral to the medicament which is placed in inhaler (70). The material may be selected from those which will not develop an electrostatic charge which would attract the medicament particles. For example, inhaler (70) may be manufactured from nylon. Alternately, an electrostatically neutral liner or coating may be placed in inhaler (70). In addition, stoppers (78) are also preferably made of an air impervious or air impregnable material and form a airtight seal with ends (72) and (74). Accordingly, when manufactured, the inhaler has a stable internal environment which is not in air flow communication with the surrounding air.

A particulate medicament suitable for absorption into the bloodstream of a person through the lungs of the person and, preferably, through the alveoli and small airway of the person's lungs, is positioned within the inhaler (70). The medicament may be a nicotine formulation of the particle size discussed above. Preferably, the individual medicament particles may vary in size up to about 7 μm, more preferably, up to about 5 μm, and most preferably, up to about 3 μm.

Figures 3B and 3C show a method for the use of inhaler (70). As shown in Figure 3B, mouth end piece (80) may be inserted through stopper (78) at end (72) of inhaler (70). For example, stopper (78) may be a thin walled plastic or rubber member which may be punctured by mouth end piece (80). Accordingly, end (72) of inhaler (70) may itself be sized or adapted so as to be received in the mouth of a person or may be adapted to receive mouth end piece (80). Mouth end piece (80) may include one way valve (82).

Once mouth end piece (80) is inserted through stopper (78) at end (72) of inhaler (70), stopper (78) may be removed from end (74). Accordingly, end (74), inhaler (70) and mouth end piece (80) define an air conduit. When the person inhales, the medicament contained in housing (70) is transported through mouth end piece (80), through one way valve (82) and into the lungs of the person. Preferably, the air conduit is sized so as to permit an air flow rate therethrough of up to about 1 L/s upon inhalation by the person and, preferably, the airflow rate is up to about 0.5 L/s.

The inhaler may be manufactured by the steps shown in Figures 4A - 4D. As shown in Figure 4A, inhaler (70) commences as an longitudinally extending member. Filter (76) is positioned at one end of inhaler (70) and filter (84) is provided at the other end of inhaler (70). Preferably, the filters and in particular filter (76) is made from an electrostatically neutral material such as nylon. Filter (84) is sized so as to prevent large particles which may irritate the throat and upper airways from entering inhaler (70). Filter (76) is sized so as to allow minute particles which would be expelled from the lung of the person to exit therethrough while retraining in tube (70) those particles of a sufficient size which would be capable of being absorbed in the lungs of the person. Filter (84) may be sized so as to allow therethrough particles less than 7 μm, preferably less than about 5 μm, more preferably less than about 3 μm and, most preferably less than about 1 μm. Filter (76) may permit particles less than about 0.1 μm from

passing therethrough. Accordingly, when air containing a medicament travels in the direction of the arrow shown in Figure 4A from end (72) to end (74), the larger particles will not enter inhaler (70) and particles which are too small to be retained in the lungs of a person pass completely through inhaler (70). Thus, the particles which are retained in inhaler (70) may conform to the dimension of particles contained in ordinary cigarette smoke (for example 0.5 - 2 μm or more preferably 0.5 - 1 μm).

A sufficient amount of air is passed through filter (72) and (74) to insert a predetermined dosage of medicament in inhaler (70). The dosage inserted into inhaler (70) may be determined based upon the concentration of medicament in the air flow and the particle size range contained in the medicament. The medicament will tend to accumulate around filter (76). Once the predetermined dose of medicament is inserted into inhaler (70), filter (84) may be removed from inhaler (70) by cutting inhaler (70) at point (86) as shown in Figure 4B. As shown in Figure 4C, one way valve (88) may then be inserted at cut end (86) of inhaler (70). Stoppers (78) may then be inserted in ends (86) and (74).

In an alternate embodiment, the step shown in Figure 4C may be omitted and a stopper may be placed in end (86) without installing a one way valve (88). According to this embodiment, the inhaler shown in Figure 3A may be prepared. In another embodiment (not shown) Filter (84) may be part of the machine which injects medicament into inhaler (70). According to this embodiment, the machine would contain an injector (not shown) containing filter (84). The injector would be sized so as to prevent air flowing out end (72) of inhaler (70) thus forcing all of the air and entrained medicament to enter inhaler (70).

When stoppers (78) are removed, and the person inhales, inhalation will cause the medicament to exit the inhaler and enter the airways of the person. The medicament may have a tendency to stick

to the inner walls of inhaler (70) and to filter (76). Accordingly, a rapid inhalation may be required and this may cause an undesirable amount of medicament to impact upon the throat and upper airways of the person. According to a preferred embodiment of the instant invention, the medicament in inhaler (70) is agitated prior to inhalation so as to cause the medicament to draw away from the walls of inhaler (70) and filter (76). This may be achieved by the person shaking inhaler (70) prior to removing stopper (78) and inhaling. Alternately, the medicament in inhaler (70) may be at sub-atmospheric pressure. When one of stoppers (78) is removed, and preferably stopper (78) located at end (74), the in rush of air will cause the medicament to fill inhaler (70). Accordingly, when the other stopper (78) is removed, the person may inhale in a controlled, slow manner so as to draw all of the medicament into the lungs of the person.

Inhaler (70) may be used with any particular medicament, including a nicotine compound as discussed herein. Inhaler (70) provides a simple method of providing a controlled dose of a medicament into the alveoli and small airways of the person's lung without any significant deposition of same in the throat and upper airways which may result in irritation of the throat and upper airways and a reduction in the amount of medicament which is actually absorbed into the bloodstream of the person.

Due to the design of inhaler (70) a relatively large dose of medicament may be placed in inhaler (70). Due to the low momentum which is imparted to the medicament as it leaves inhaler (70) and enters the person's mouth, a large dose of medicament may be inhaled in a single breath. Depending upon the medicament and the dosage which may be required, it is appreciated that it may not be possible, even with the use of inhaler (70) for a person to inhale a full dosage without causing some irritation to the person's throat and upper airways. If the amount of the dosage is sufficiently high, then two or more inhalers (70) may be utilized by the person to achieve a full dose.

Alternately, inhaler (70) may be designed to contain a full dose of medicament but, due to the use of dilution air, several breaths may be required to inhale all of the medicament in inhaler (70). For example, inhaler (70) which is shown in Figure 5A is similar to the inhaler shown in Figure 4D. Accordingly, inhaler (70) has a filter (76) located adjacent end (74) in addition, one way valve (88), which opens at sub-atmospheric pressure, is positioned adjacent end (72). End (72) is sealed by stopper (78). Medicament (90) is generally represented as being located near or on filter (76). As discussed above, if inhaler (70) is manufactured according to the steps set out in Figures 4A - 4D, the medicament will tend to accumulate near or adjacent filter (76).

In order to restrict the amount of air which may be drawn through inhaler (70) with any inhalation, inhaler (70) is provided with end member (92) positioned at end (74) of inhaler (70) and one or more by-pass valve (98). End member (92) seals end (74) of inhaler (70). End member (92) may be formed as an integral part of inhaler (70). End member (92) has longitudinally extending member (94) which is sealed by releasable seal (96). Similarly, by-pass valve (98) is sealed by releasable seal (100).

As discussed above, the medicament in inhaler (70) is preferably agitated so as to disperse medicament (90) throughout inhaler (70) prior to inhalation. One way to achieve this is to manufacture inhaler (78) to be at sub-atmospheric pressure. If this method is utilized, one of the releasable seals may be removed thus allowing air to enter inhaler (70) as shown in Figure 5B. The in rush of air disperses medicament (90) throughout inhaler (70). Subsequently, as shown in Figure 5C, stopper (78) may be removed. Subsequently, as shown in Figure 5D, releasable seal (100) may be removed. Thus, when the person inhales, air is drawn through member (94), through inhaler (70) and through one way valve (88) into the airways of the person. Simultaneously, air enters by-pass valve (98) thus diluting the concentration of medicament (90) in the air inhaled by the person.

Thus, more than one inhalation is required to withdraw all of the medicament from inhaler (70).

By varying the number and size of by-pass valves (98), as well as the size of member (94), the amount of air which flows through inhaler (70) as opposed to by-pass valve (98) may be adjusted thereby controlling the number of inhalations which may be required to withdraw all of the medicament from inhaler (70). Alternately, other modifications may be utilized to control the amount of medicament which is withdrawn from inhaler (70). For example, end member (92) may be replaced by a variable aperture which controls the amount of air which may pass through inhaler (70).

If the medicament in inhaler (70) is nicotine, inhaler (70) may be designed to look like a cigarette. In addition, by appropriately dimensioning by-pass valves (98) and member (94), inhaler (70) may contain an amount of nicotine which is contained in a cigarette. Several inhalations (i.e. puffs) would be required to withdraw all of the medicament in stages from inhaler (70). Thus, not only would the person use inhaler (70) in the same manner as they would smoke a cigarette, but the transportation of nicotine into the person and the absorbtion thereof in the lungs of the person would more closely simulate smoking.

WE CLAIM:

1. A method of delivering a medicament including at least one nicotine formulation to a person comprising introducing a predetermined dose of a medicament including at least one nicotine formulation suitable for absorption into the bloodstream of the person through the alveoli and lower airways of the person's lungs, from a portable inhaler into the alveoli and lower airways of the person's lungs.

2. A method as claimed in claim 1 wherein the formulation is suitable for absorption into the bloodstream of the person through the alveoli and small airways of the person's lungs and the medicament is introduced into the alveoli and small airways of the person's lungs.

3. A method as claimed in claim 1 wherein the predetermined dose comprises from about 0.1 to about 10 mg of nicotine.

4. A method as claimed in claim 1 wherein the predetermined dose comprises from about 0.2 to about 2 mg of nicotine.

5. A method as claimed in claim 1 wherein the predetermined dose comprises from about 0.1 to about 0.5 mg of nicotine.

6. A method as claimed in claim 1 wherein said medicament, upon entry into the airways of the person, includes medicament particles which vary in size up to about 10 μm.

7. A method as claimed in claim 1 wherein said medicament, upon entry into the airways of the person, includes medicament particles which vary in size up to about 5 μm.

8. A method as claimed in claim 1 wherein said medicament, upon entry into the airways of the person, includes medicament particles which vary in size up to about 3 μm.

9. A method as claimed in claim 1 wherein the medicament additionally comprises a pharmaceutically acceptable carrier, excipient, or diluent.

10. A method as claimed in claim 7 wherein said inhaler has an air conduit which is sized to permit an air flow rate therethrough of up to about 2 L/s upon inhalation by the person.

11. A method as claimed in claim 7 wherein said inhaler has an air conduit which is sized to permit an air flow rate therethrough of up to about 0.5 L/s upon inhalation by the person.

12. A method as claimed in claim 7 wherein said method is repeated at time intervals sufficient to reduce the negative effects of nicotine withdrawal.

13. A method as claimed in claim 1 and including the step, after introducing said medicament, of preventing said inhaler from introducing a further dosage of said medicament into the person's lung until a timed interval has elapsed.

14. A method as claimed in claim 1 wherein the introduction of said predetermined dose is used as a replacement for tobacco or tobacco substitutes.

15. A method as claimed in claim 1 wherein the introduction of said predetermined dose is used to assist the person to withdraw from nicotine dependency.

16. A method as claimed in claim 1 wherein said inhaler is a low velocity release inhaler.

17. A method as claimed in claim 1 wherein, upon activation of said inhaler, said medicament is released from a container and, upon inhalation by the person, said medicament is dispersed by the said person's breath.

18. A method as claimed in claim 17 wherein said inhaler includes means to mechanically assist the dispersion of said medicament and said method includes the step of mechanically assisting such dispersion.

19. A method as claimed in claim 18 wherein said means to mechanically assist the dispersion includes mixing means adapted to disperse said particles as the person inhales.

20. A method as claimed in claim 19 wherein said mixing means comprises a non-rotatably mounted impeller and, as the person inhales, the inhalation causes air to entrain the medicament and cause the medicament to flow past said impeller to assist in the dispersion of said medicament.

21. A method as claimed in claim 19 wherein said mixing means comprises a rotatably mounted impeller and, as the person inhales, the inhalation causes air to entrain the medicament and cause the medicament to flow past said rotating impeller to assist in the dispersion of said medicament.

22. A method as claimed in claim 21 wherein the rotation of said impeller is assisted by mechanical means.

23. A method as claimed in claim 21 wherein the rotation of said impeller is driven by battery operated motor means.

24. A method as claimed in claim 1 wherein, upon activation of said inhaler, said medicament is released from a pressurized container into the air at a

velocity sufficiently slow to be entrained in the air inhaled by the user.

25. A method as claimed in claim 1 wherein said medicament is a particulate medicament.

26. A method as claimed in claim 1 wherein said introduction of said nicotine formulation is used to assist the person to withdraw from cigarette dependency.

27. A method as claimed in claim 1 wherein said introduction of said nicotine formulation is used to provide nicotine to supply the person's tobacco smoking induced nicotine dependency.

28. A method of introducing a medicament comprising at least one nicotine formulation into the lungs of a patient using a portable inhaler having a housing having a first opening and a second opening, one of said first opening and said second opening being adapted to deliver the medicament to the mouth of the person and storage means for storing a medicament suitable for absorption into the bloodstream of the person through the alveoli and lower airways of the patient's lungs, said method comprising the steps of:

(a) releasing said medicament from said storage means;

(b) dispersing said medicament for inhalation by the person; and,

(c) inhaling said medicament

said medicament being at a velocity sufficiently slow prior to said inhalation to be entrained in the air upon inhalation by the person.

29. A method as claimed in claim 28 wherein the formulation is suitable for absorption into the bloodstream of the person through the alveoli and small airways of the person's lungs and the medicament is introduced into the alveoli and small airways of the person's lungs.

30. A method as claimed in claim 28 wherein said inhaler includes means to

mechanically assist the dispersion of said medicament and said method includes the step of mechanically assisting such dispersion.

31. A method as claimed in claim 30 wherein said means to mechanically assist the dispersion includes mixing means adapted to impart disperse said particles as the person inhales.

32. A method as claimed in claim 31 wherein said mixing means comprises a non-rotatably mounted impeller and, as the person inhales, the inhalation causes air to entrain the medicament and cause the medicament to flow past said impeller to assist in the dispersion of said medicament.

33. A method as claimed in claim 31 wherein said mixing means comprises a rotatably mounted impeller and, as the person inhales, the inhalation causes air to entrain the medicament and cause the medicament to flow past said rotating impeller to assist in the dispersion of said medicament.

34. A method as claimed in claim 33 wherein the rotation of said impeller is assisted by mechanical means.

35. A method as claimed in claim 28 wherein said medicament is under pressure in said storage means and said medicament is at least partially dispersed by releasing said medicament from said storage means.

36. A method of introducing a medicament into the lungs of a person using a portable inhaler having a housing having a first opening and a second opening, one of said first opening and said second opening being adapted to deliver the medicament to the mouth of the person and container means for receiving a medicament suitable for absorption into the bloodstream of the person through the alveoli and lower airways of the patient's lungs, said method comprising the steps of:

(a) delivering said medicament to said container means

(b) dispersing said medicament for inhalation by the person; and,

(c) inhaling said medicament

said medicament being at a velocity sufficiently slow prior to said inhalation to be entrained in the air upon inhalation by the person.

37. A method as claimed in claim 36 wherein the formulation is suitable for absorption into the bloodstream of the person through the alveoli and small airways of the person's lungs and the medicament is introduced into the alveoli and small airways of the person's lungs.

38. A method as claimed in claim 36 wherein said inhaler includes means to mechanically assist the dispersion of said medicament and said method includes the step of mechanically assisting such dispersion.

39. A method as claimed in claim 38 wherein said means to mechanically assist the dispersion includes mixing means adapted to disperse said particles as the person inhales.

40. A method as claimed in claim 38 wherein said mixing means comprises a non-rotatably mounted impeller and, as the person inhales, the inhalation causes air to entrain the medicament and cause the medicament to flow past said impeller to assist in the dispersion of said medicament.

41. A method as claimed in claim 38 wherein said mixing means comprises a rotatably mounted impeller and, as the person inhales, the inhalation causes air to entrain the medicament and cause the medicament to flow past said rotating impeller to assist in the dispersion of said medicament.

42. A method as claimed in claim 40 wherein the rotation of said impeller is assisted by mechanical means.

43. A method as claimed in claim 38 wherein said medicament is under pressure in said storage means and said medicament is at least partially dispersed by releasing said medicament from said storage means.

44. A method as claimed in claim 38 wherein said inhaler is a low velocity release inhaler.

45. A method of manufacturing a portable inhaler for use by a person to introduce a medicament into the patient's lungs, said inhaler having a housing with a first opening and a second opening, one of said first opening and said second opening being adapted to deliver the medicament to the mouth of the person comprising the steps of:

(a) placing said housing between first and second filter means;

(b) passing a fluid containing entrained medicament through said first filter means and said second filter means, to deposit said medicament in said housing; and

(c) sealing said first and said second openings, said first filter means being adapted to remove from said fluid particles of the medicament which are sufficiently large to irritate the throat and upper airways of the person, said second filter means being adapted to pass therethrough said fluid and particles which are sufficiently small that they would not be absorbed in the lungs of the person.

46. The method as claimed in claim 45 wherein said second filter means comprises part of said housing.

47. The method as claimed in claim 45 wherein step (b) is conducted at subatmospheric pressure.

48. The method as claimed in claim 45 wherein subsequent to step (b) fluid is

removed from said housing so that, when said housing is sealed, the fluid in said housing is at subatmospheric pressure.

49. A method of assisting a person to withdraw from cigarette dependency comprising introducing a predetermined dose of a non-pressurized, particulate medicament comprising at least one nicotine formulation suitable for absorption into the bloodstream of the person through the alveoli and small airways of the person's lungs, from a breath activated inhaler into the alveoli and small airways of the person's lungs.

50. A method as claimed in claim 49 wherein the predetermined dose is from about 0.1 to about 10 mg of nicotine.

51. A method as claimed in claim 49 wherein the predetermined dose is from about 0.2 to about 2 mg of nicotine.

52. A method as claimed in claim 49 wherein the predetermined dose is from about 0.1 to about 0.5 mg of nicotine.

53. A method as claimed in claim 49 wherein said individual medicament particles vary in size up to about 5 μm.

54. A method as claimed in claim 49 wherein the individual medicament particles vary in size up to about 2 μm.

55. A method as claimed in claim 49 wherein the medicament additionally comprises a pharmaceutically acceptable carrier, excipient, or diluent.

56. A method as claimed in claim 53 wherein said inhaler has an air conduit which is sized to permit an air flow rate therethrough of up to about 1 L/s upon inhalation by the patient.

57. A method as claimed in claim 53 wherein said inhaler has an air conduit which is sized to permit an air flow rate therethrough of up to about 0.5 L/s upon inhalation by the patient.

58. A method as claimed in claim 53 wherein said method is repeated at time intervals sufficient to reduce the negative effects of nicotine withdrawal.

59. A method as claimed in claim 49 and including the step, after introducing said medicament, of preventing said inhaler from introducing a further dosage of said medicament into said person's lung until a timed interval has elapsed.

60. A method as claimed in claim 49 wherein the introduction of said predetermined dose is used as a tobacco substitute.

61. A method as claimed in claim 49 wherein the introduction of said predetermined dose is used to assist the person to withdraw from nicotine dependency.

62. A method as claimed in claim 49 wherein said medicament is dispersed in said person's breath and including the step of mechanically affixing such dispersion.

63. A method of providing nicotine to supply a person's tobacco smoking induced nicotine dependency comprising introducing a predetermined dose of a non-pressurized, particulate medicament comprising at least one nicotine formulation suitable for absorption into the bloodstream of the person through the alveoli and small airways of the person's lungs, from a breath activated inhaler into the alveoli and small airways of the person's lungs.

64. A method as claimed in claim 63 wherein the predetermined dose is from

about 0.1 to about 10 mg of nicotine.

65. A method as claimed in claim 63 wherein the predetermined dose is from about 0.2 to about 2 mg of nicotine.

66. A method as claimed in claim 63 wherein the predetermined dose is from about 0.1 to about 0.5 mg of nicotine.

67. A method as claimed in claim 63 wherein said individual medicament particles vary in size up to about 5 μm.

68. A method as claimed in claim 63 wherein the individual medicament particles vary in size up to about 2 μm.

69. A method as claimed in claim 63 wherein the medicament additionally comprises a pharmaceutically acceptable carrier, excipient, or diluent.

70. A method as claimed in claim 67 wherein said inhaler has an air conduit which is sized to permit an air flow rate therethrough of up to about 1 L/s upon inhalation by the patient.

71. A method as claimed in claim 67 wherein said inhaler has an air conduit which is sized to permit an air flow rate therethrough of up to about 0.5 L/s upon inhalation by the patient.

72. A method as claimed in claim 67 wherein said method is repeated at time intervals sufficient to reduce the negative effects of nicotine withdrawal.

73. A method as claimed in claim 63 and including the step, after introducing said medicament, of prevent said inhaler from introducing a further dosage of said medicament into said person's lung until a timed interval has elapsed.

74. A method of assisting a person to withdraw from tobacco induced nicotine dependency, comprising introducing a predetermined dose of a non-pressurized, particulate medicament comprising at least one nicotine formulation suitable for absorption into the bloodstream of the person through the alveoli and small airways of the person's lungs into a breath activated inhaler for use by said person as a cigarette substitute.

75. A method as claimed in claim 74 wherein the predetermined dose is from about 0.1 to about 10 mg of nicotine.

76. A method as claimed in claim 74 wherein the predetermined dose is from about 0.2 to about 2 mg of nicotine.

77. A method as claimed in claim 74 wherein the predetermined dose is from about 0.1 to about 0.5 mg of nicotine.

78. A method as claimed in claim 74 wherein said individual medicament particles vary in size up to about 5 μm.

79. A method as claimed in claim 74 wherein the individual medicament particles vary in size up to about 2 μm.

80. A method as claimed in claim 74 wherein the medicament additionally comprises a pharmaceutically acceptable carrier, excipient, or diluent.

81. A method as claimed in claim 78 wherein said inhaler has an air conduit which is sized to permit an air flow rate therethrough of up to about 1 L/s upon inhalation by the patient.

82. A method as claimed in claim 78 wherein said inhaler has an air conduit

which is sized to permit an air flow rate therethrough of up to about 0.5 L/s upon inhalation by the patient.

83. A method as claimed in claim 78 wherein said method is repeated at time intervals sufficient to reduce the negative effects of nicotine withdrawal.

84. A method as claimed in claim 74 and including the step, after introducing said medicament, of prevent said inhaler from introducing a further dosage of said medicament into said person's lung until a timed interval has elapsed.

85. A method of introducing a medicament into the lungs of a patient using a breath activated inhaler having a housing having a first opening and a second opening, said first opening and said second opening being releasably sealed, one of said first opening and said second opening being adapted to deliver the medicament to the mouth of the patient; and, a non-pressurized, particulate medicament suitable for absorption into the bloodstream of the patient through the alveoli and small airways of the patient's lungs positioned in said housing, said method comprising the steps of:

(a) agitating said medicament in said housing to disperse said medicament throughout said housing;

(b) releasing said seals on said first and second openings; and

(c) inhaling said medicament

said medicament being under sub-atmospheric pressure in said sealed housing and said medicament being dispersed by releasing said seal on said other of said first and second openings.

86. The method as claimed in claim 85 wherein said individual medicament particles vary in size up to about 2 μm.

87. The method as claimed in claim 86 wherein said individual medicament particles vary in size up to about 1 μm.

88. The method as claimed in claim 85 wherein, when said seals are removed, said first and second openings and said housing define an air conduit and said air conduit is sized to permit an air flow rate therethrough of up to about 1 L/s upon inhalation by the patient.

89. The method as claimed in claim 88 wherein, when said seals are removed, said first and second openings and said housing define an air conduit and said air conduit is sized to permit an air flow rate therethrough of up to about 0.5 L/s upon inhalation by the patient.

90. The method as claimed in claim 85 wherein, the breath activated inhaler includes by-pass air feed means for supplying air to dilute the air passing through said housing so as to reduce the concentration of the medicament in the air which is inhaled by the patient.

91. The method as claimed in claim 90 wherein said by-pass air feed means is located near said one of said first opening and said second opening which is adapted to deliver the medicament to the mouth of the patient.

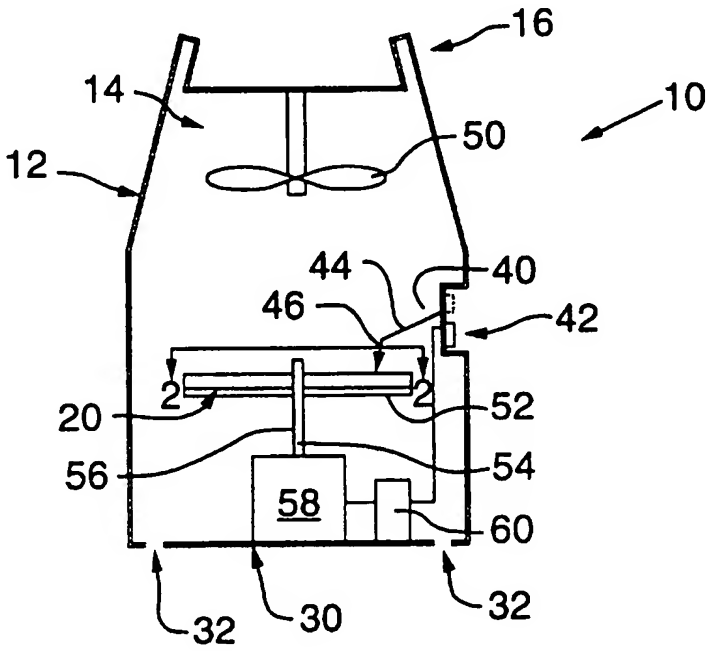

FIG.1

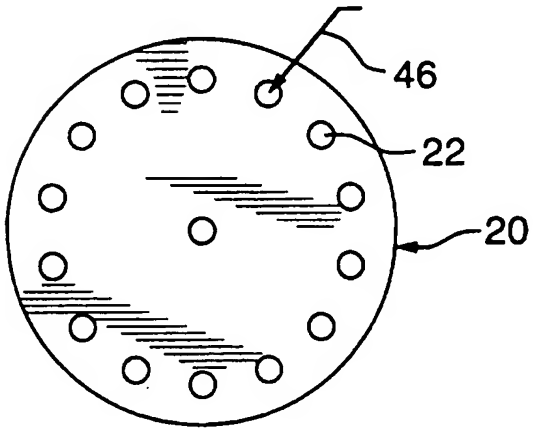

FIG.2

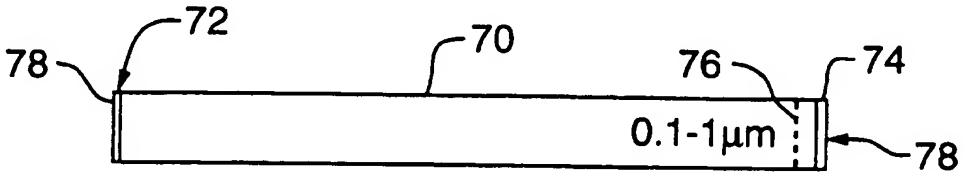

FIG.3A

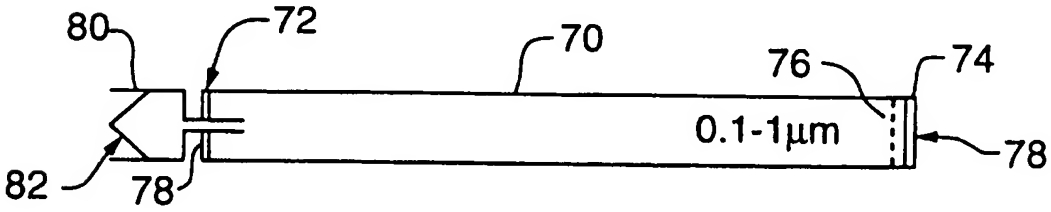

FIG.3B

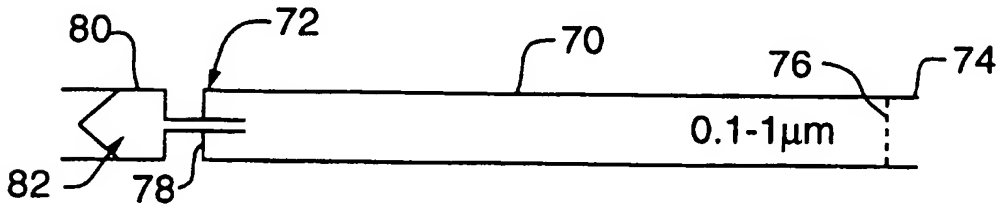

FIG.3C

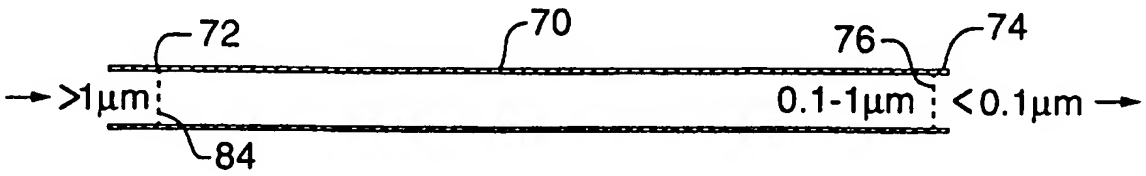

FIG.4A

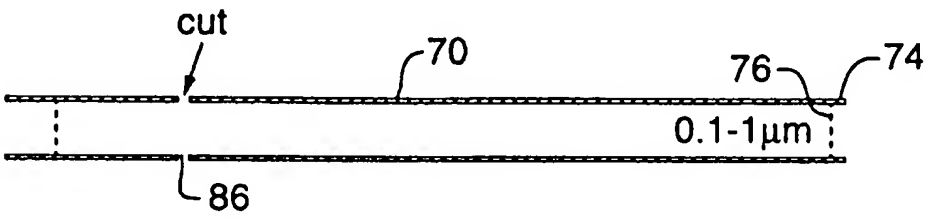

FIG.4B

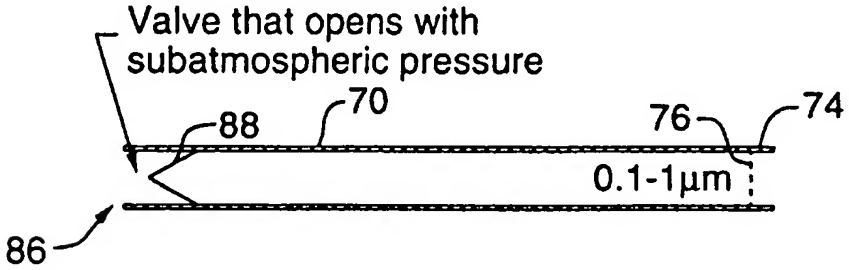

FIG.4C

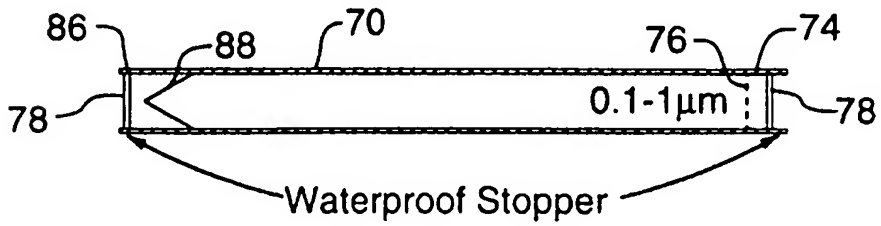

FIG.4D

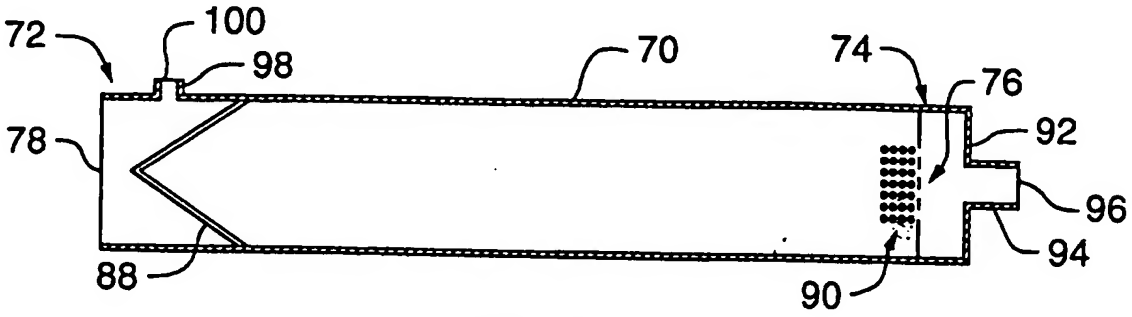

FIG.5A

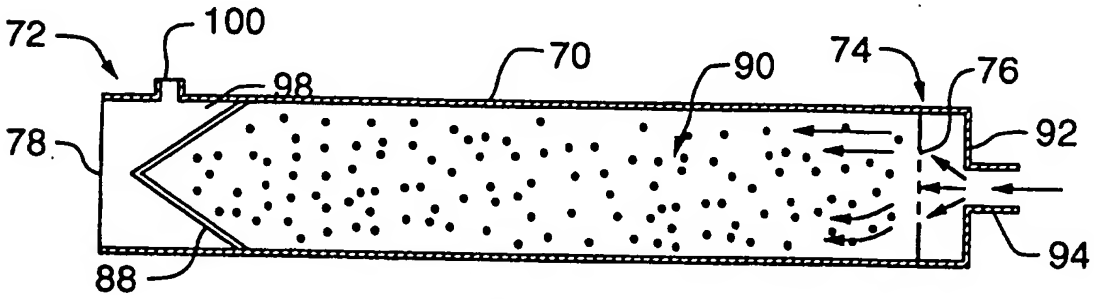

FIG.5B

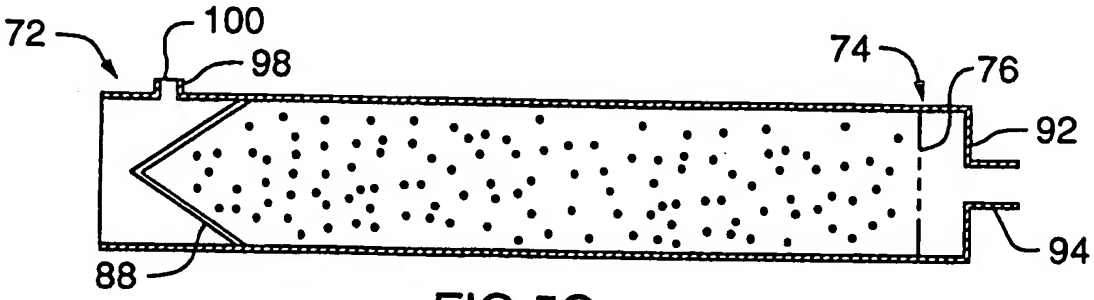

FIG.5C

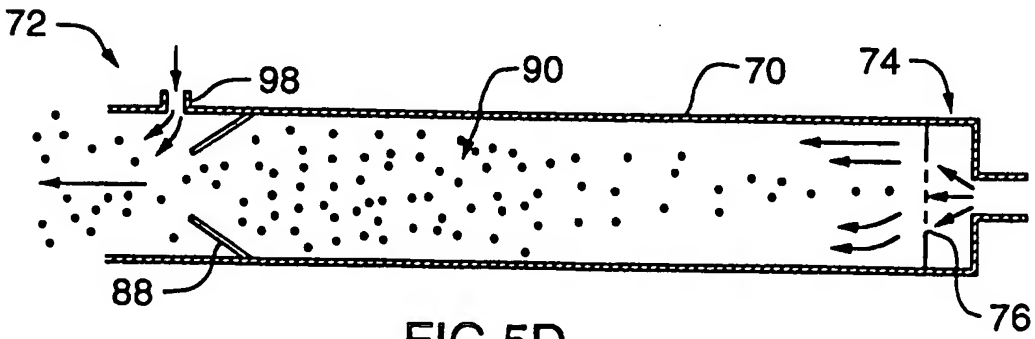

FIG.5D

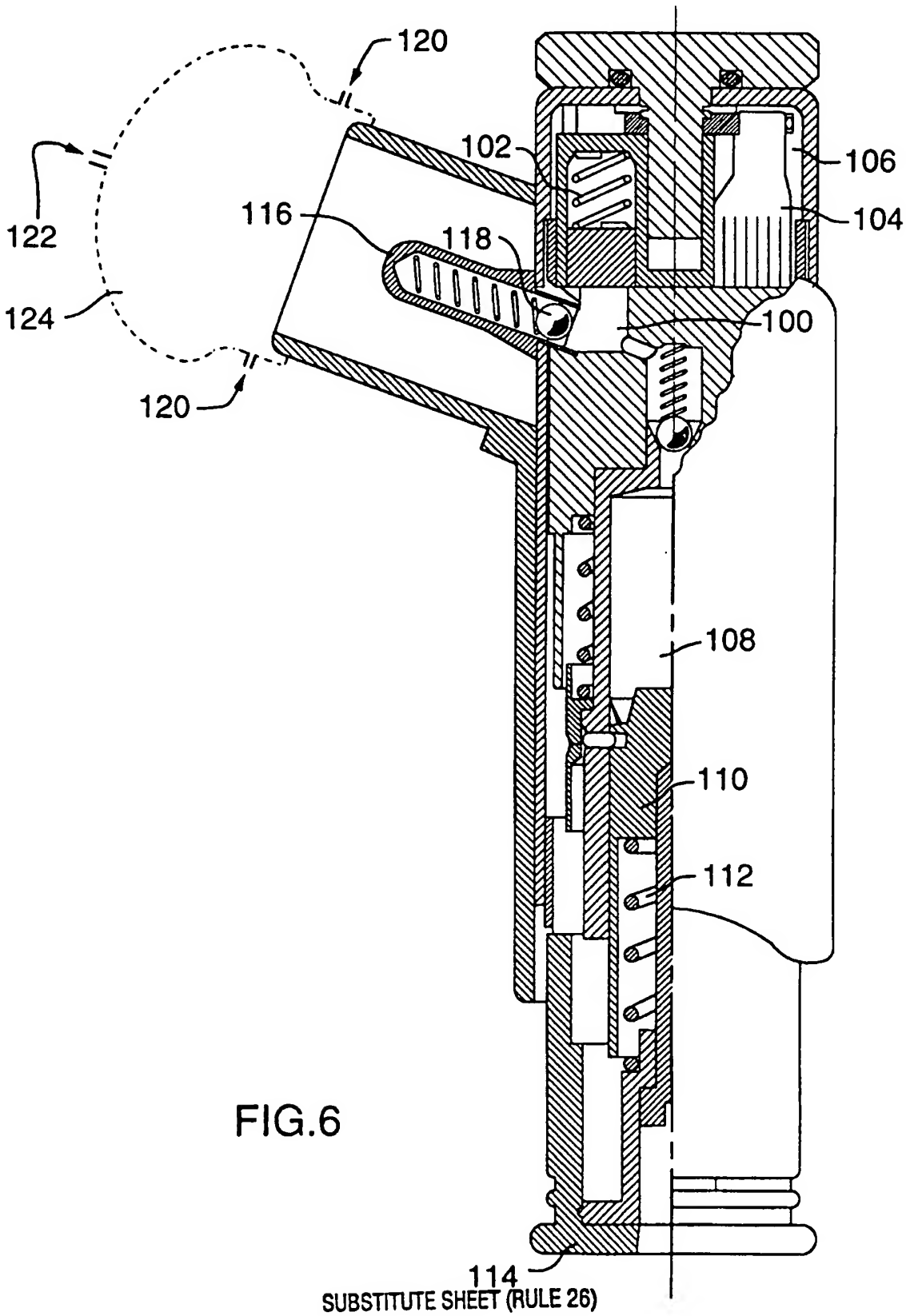

FIG.6

INTERNATIONAL SEARCH REPORT

In ational Application No
PCT/CA 95/00562

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61M15/06 A61M15/00 A61K9/00 A24F47/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61M A24F A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US,A,5 441 060 (ROSE ET AL.) 15 August 1995 see abstract; figures	45-48
A	US,A,4 655 229 (SENSABAUGH ET AL.) 7 April 1987 see abstract; figures	45-48

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

2

Date of the actual completion of the international search	Date of mailing of the international search report
17 May 1996	06.06.96

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax (+ 31-70) 340-3016	Villeneuve, J-M

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CA95/00562

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 1-44,49-91
because they relate to subject matter not required to be searched by this Authority, namely:
PCT Rule 39.1 (iv)

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Int. ational Application No
PCT/CA 95/00562

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
US-A-5441060	15-08-95	AU-B-	6171994	29-08-94
		EP-A-	0683632	29-11-95
		WO-A-	9417679	18-08-94
US-A-4655229	07-04-87	AU-B-	3664184	08-08-85
		CA-A-	1227713	06-10-87
		EP-A-	0150810	07-08-85
		JP-A-	60192581	01-10-85